UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,924	02/25/2004	Ben-Zion Dolitzky	1662/568078	9231

7590 07/10/2008

Kenyon & Kenyon
One Broadway
New York, NY 10004

EXAMINER	
CHANG, CELIA C	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
07/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,924	DOLITZKY ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *4-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a RCE of SN 10/788,924.

Claims 1-3 and 14-16 reading on 1-3 are examined. Claims 4-13 and remaining subject matter of claims 14-16 are withdrawn from consideration per 37 CFR 1.142(b).

2. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

On page 12 of the specification, it was described Fexofenadine hydrochloride Form IX is a solvate of cyclcohexane or MTBE. It is unclear, what is the subject matter of claims 1-3. Is it fexofenadine hydrochloride form IX? Is it fexofenadine hydrochloride having PXRD of claim 1 or is it fexofenadine hydrochloride having PXRD of fig. 6. Please note that it is very clear from the understanding of a crystal chemist that solvates are different "material" from its non-solvated material (see Seddon) and there should never be any doubt, in this century, about the chemical identity of a material. PXRD although useful in delineating crystalline structure, does not offer reliable information on chemical identity of a material. It is well recognized in the art that powdered X-ray diffraction can be drastically different from its single crystal X-ray (see Bernstein p.118) and identical PXRD would be obtained for *different* chemical material were the crystalline structures are identical (see Bernstein p.372). Further, powdered X-ray diffractogram are well known to contain artifacts. Therefore, in absence of extensive study and correction, "…preferred orientation has significant potential to misguide the analyst……that changes in the powder X-ray pattern resulted from experimental artifacts rather than polymorphism….." (Davidovich p.16).

In view of the prior art from above, it is very confusing as to what is being claimed in claims 1-3, any fexofenadin currently measured or to be measured in the future, irrespective of chemical identity, having any of the lines of some of the lines of claim 1, or having the pattern of fig. 6 or is "called" form IX. Are they cyclohexan solvate of fexofenadine hydrochloride or MTBE solvate of fexofenadine hydrochloride with the specific crystalline structure? Is Form IX

the same or different material from cyclohexane or MTBE solvates? The claims are indefinite and confusing.

Applicants argued that "A person skilled in the art would readily understand that claim 1 is drawn to a crystalline form of fexofenadine hydrochloride characterized by the powder [power] X-ray diffraction(PXRD) peaks recited in the claim" on page 2 is *self conflicting* with applicants' own argument on page 4 wherein it was stated "As disclosed in page 12, lines 11-16, fexofenadine hydrochloride Form IX is a solvate of cyclohexane or MTBE". The ambiguity is self evidenced, which is the product of claim 1? Is it fexofenadine hydrochloride or is it fexofenadine hydrochloride cyclohexane solvate or is it fexofenadine hydrochloride MTBE solvate? Please note that in the chemical art fexofenadine hydrochloride, fexefenadine hydrochloride cyclohexane solvate and fexofenadine hydrochloride MTBE solvate are all *different chemical identities*. It has been clearly stated by Seddon in the prior art reference recited on PTO-892 that "Now, as there should never be any doubt, *in this century*, about the chemical identity of a material, then it follows that solvates of a compound can never be pseudopolymorphs [of a compound], as there will never be any doubt as to their chemical identity". In addition, a material cannot be separated from ***all*** it's properties, applicants has not produced a material that has only fexofenadine hydrochloride *without the hexane or MTBE* that is crystalline and has the recited PXRD or any material that has only fexofenadine hydrochloride *without the hexane or MTBE* has the PXRD without the DTG profile.

The ambiguity as to "what" is claim 1 is self evident.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Ortyl et al. US 5,738,872.

See col. 30, table 19, every peak of the instant claims are found in the table using approximate conversion between D-space and 2θ. For example, instant 2θ 9.3, 17.4, 18.2, 19.4, 19.6, 21.6 and 24.0 $\pm$0.2 corresponding to D-space of table 19 as 11.41, 5,23, 5.14, 4.72, 4.40, 4.18, 3.85. Therefore, by PXRD alone, the same peaks are found i.e. identical pattern. Please

note that claims are drawn to material, anticipation is found if identical material is found. There is no limitation as to how many of the peaks must be there to represent identical material. In the instant case, the prior art although disclosed many peaks, most of the claimed peaks are found in table 19, therefore, anticipation of same material.

Applicants argued that by conversion of Ortyl's table 19, it appeared that there are different peaks in the instant PXRD and the Ortyl table.

Please note that on powder X-ray diffraction data, absent of side by side comparison (measured by the same laboratory, machine and conditions), artifacts can suppress data to a single peak (Berstein p.118). The office has employed art recognized standard that for a material having identical chemical identity, *at least* one identical peak existed between the prior art PXRD constitutes *same identical product*. Please note in comparing with the instant claims, seven peaks were clearly identified supra. Please note that the claims are identical in chemical identity from the prior art, identical in seven peaks of the PXRD with understanding by the state of the art that the different peaks being contributed by artifacts, anticipation was found. US pharmacopia clearly warned artisan in the field that minor difference does not confirm "polymorph" without careful factual evaluation. The mere allegation that there differences by attorney does not provide side by side comparison showing no artifacts in inter-laboratory data collection etc.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ortyl et al. US 5,738,872 in view of Evans, and US Pharmacopia and Brittain supplemented with Gottlieb.

Determination of the scope and content of the prior art (MPEP §2141.01)

Ortyl et al. '872 disclosed crystalline fexofenadine hydrochloride as delineated supra. Processes of making such crystals employed acetone solution and crystallization from ethylacetate (see col. 27, line 25- col. 28, line 5).

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claimed product and the prior art is that some solvents were included in the claimed crystals and different X-ray diffraction peaks were observed. Evans taught that for crystalline organic material, it is prima facie obvious for those with suitable interstitial space to entrap solvents. The entrapment is purely mechanical thus does not constitute any new crystalline forms (Evans p.396). US Pharmacopia disclosed that solvates of a known compound may display different X-ray diffraction pattern but whether they are true polymorphs must be evaluated carefully. Britain et al. taught, many organic crystalline compounds can form crystalline solvates, which can be obtained using ordinary laboratory solvents. Gottlieb taught the cyclohexan and MTBE are ordinary laboratory solvents.

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references placed the crystalline fexofenadine hydrochloride in the artisan's possession. One having ordinary skill in the art would be motivated to prepare such crystalline compound with ordinary laboratory solvents instead of ethylacetate of the prior art with the expectation to obtain crystalline solvates of the known crystal. Such crystalline solvates are expected to have similar properties as the known crystal (Evans p.396) with small differences in X-ray diffraction patterns (US pharmacopia). Therefore, the instantly claimed product is prima facie obvious variations expected of the prior art product, by picking and choosing alternative solvents conventional to one skilled in the art with its expected outcome of such alternative solvents.

In so far as the instant claims are concerned, the material of the claims, *fexofenadine hydrochloride crystal*, is identical to the Ortyl's material. The difference between the more limited claims and the process of employing a different solvent such as cyclohexane or MTBE, are routine choices by one having ordinary skill in the chemical art, thus, the inclusion of such impurity of solvents in the final product is nothing more than routine inclusion of Ortyl's product of minor impurity. Especially, attorney argued that the instant claims are not drawn to *different chemical identity* but the same "fexofenadine hydrochloride" as Ortyl's with different inclusion showing as different lines in XPRD. Impurities and results caused by impurities are within the sphere of invention as disclosed by the prior art (see Evans). The teaching of fexofenadine

hydrochloride crystal of the prior art is chemically identical (teaching), the *suggestion* that organic crystals which are chlathrates can included common laboratory solvents and the *motivation* of employing different solvent to obtain stable (less mechanical constrain) crystals are all within the knowledge and technique of one having ordinary skill. Thus, establishing a prima facie case of obviousness. Applicants provided no evidence that why employing an alternative common laboratory solvent would not produce the same product with a little different impurity. Please note that the claims and the prior art are the *same identical material*.

5. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

The analysis is applied to the instant case.

Nature of invention

The claim is drawn to a pharmaceutical composition containing a particular crystalline form of the drug fexofenadine hydrochloride.

The state of the art and predictability

The state of the art in preparing pharmaceutical composition containing specific crystalline form is highly unpredictable (see Doelker et al. or Rouhi). It is conventional expectation that polymorphic forms of crystals are metastable which will convert to the thermodynamically stable form upon formulation (see Doelker abstract).

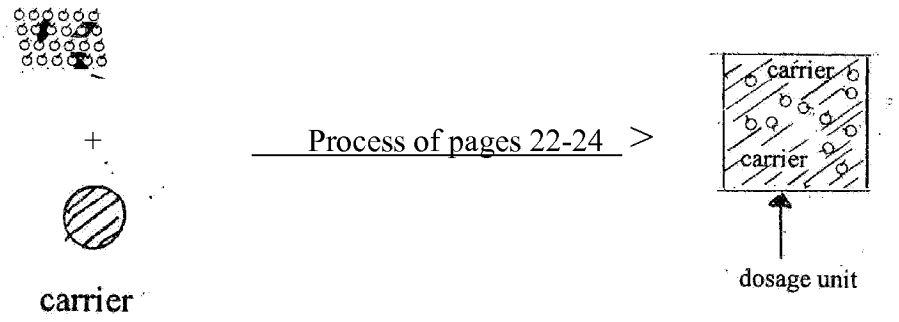
The amount of guidance and working examples

The specification on pages 22-26 provided description of pharmaceutical composition containing the claimed crystalline form with conventional process in milling, grinding, tabletting, granulation, etc. for which have been well recognized in the art to promote polymorphic transformation (see Doelker abstract). No example or information as to the prepared tablet for example to maintain the claimed crystalline form i.e. same X-ray diffractogram. One skilled in the art knowing the high degree of unpredictability and the conditions for crystal transformation during processing have not been given sufficient particularity of how the specific crystalline form can be maintained in a composition, especially, the composition includes liquid for which all crystalline form is abolished.

It was clearly delineated with state-of-the-art references that the "predictable" result of pharmaceutical formulation is the formation of the thermodynamically stable form of any pharmaceutical material. On pages 22-24, the process of making the instant pharmaceutical composition which are routine formulation using processes such as liquid formulation, wet dispersion etc. for which clearly transforming of any crystalline form is *evidenced*.

That is:

Fexofenadine HCl form IX



Containing scattered material

Please note that any composition liquid or solid containing a "crystalline" form was neither described i.e. using what carrier; nor enabled, i.e. a composition containing the same X-ray diffraction pattern of the specific crystals.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by US 4,254,129 see claim 11, 9 and compounds of examples 2-3, in view of Rowland et al.

The compound of the claim is found in examples 2-3 of Carr et al. '129 wherein the small genus of fexofenadine and hydrochloride salts found in examples 2-3 renders the claimed product anticipated. The method of therapy using the compound would be expected to be at physiological environment. Under physiological environment which is aqueous solution, all crystalline forms are abolished, thus, using the instant crystal would be identical to using the thermodynamically stable form of the same compound.

Initially, applicants attention is drawn to applicants' argument that the claimed "material" is the *identical* chemical compound fexofenadine hydrochloride as the prior art just of a different form. Even if the product contains impurity such as solvents, the process of treatment would be identical using identical material.

It was evidenced in the conventional teaching in the physiology of the human body that dissolution of the solvate can occur at several stages of drug kinetics (see p.23-24 specification). The first location is in the formulation stage wherein a liquid dosage such as injection ample, liquid capsule etc. was employed (see pages 23-24 specification), then the active ingredient being administer is the dissoluted compound fexofenadine hydrochloride.

In this scenario, anticipation is found since both the active ingredient and its out come is identical to the prior art.

The other location of dissolution can be expect at either the absorption and distribution stage (see Rowland and Tozer) or at the cellular level wherein receptor binding is occurring. Either stage of the claimed process would be a prima facie obvious modification of the prior art process employed by Carr et al. '129 because one skilled in the pharmaceutical art would expect *if the solvates had any different solubility or bioavailability,* the efficacy is slightly different from the non-solvated form, thus, the same process of use with an innate efficacy outcome. IN the instant case, *there is no description or evidence that any bioavailability issue was found in the specification*. Therefore, since after physiological deslvation, the same material and the same effect was the process evidence, anticipation was found.

Please note that applicants' argument with respect to PXRD peaks is irrelevant at the claimed process of physiological steps effecting receptor outcome. The material, the dosage and the efficacy are all identical to the prior art.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
July 1, 2008

/Celia Chang/
Primary Examiner
Art Unit 1625